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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/646,835	01/11/2001	Gabriele Multhoff	105032-991230	1173

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1642	24

DATE MAILED: 09/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/646,835	Applicant(s) MULTHOFF, GABRIELE	
	Examiner Karen A Canella	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *31-43,45-56 and 58-60* is/are pending in the application.

4a) Of the above claim(s) *49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *31-43,45-48,50-56 and 58-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

KAC
9/25/03

DETAILED ACTION

1. Claims 44 and 57 have been canceled. Claims 31, 37, 45 and 58 have been amended. Claim 49, drawn only to non-elected species, is withdrawn from consideration. Claims 31-43, 45-48, 50-56, and 58-60 are under consideration. It is noted that claim 43 was inadvertently included with the claims withdrawn from consideration in the Office action of Paper No. 16, but was in fact examined to the extent that it read on cancerous diseases as indicated by the rejection of page 11, section 15 of the previous Office action..

2. Applicant's request for correction of filing receipt, filed July 3, 2001, has been entered.. Applicant's requests for correction of filing receipt, filed May 29, 2001 and January 30, 2001, are noted and will be forwarded to a PTO offical for processing.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

4. Applicant argues for the reconsideration of the election of species requirement of Paper No. 14. The species were set forth as follows:

a. cancerous diseases,
b. autoimmune diseases, and
c. infectious diseases.

Applicant argues that the art recognizes a commonality of activity by Hsp 70 and NK cells, and the art recognizes "the cytotoxicity targets" of NK cells. This has been considered but not found persuasive. As was stated in the previous Office action , "as demonstrated by the art rejections below, the claimed methods and compositions lack novelty over the art and thus claims drawn to methods of treatment comprising administering the Hsp70 protein, cells expressing said protein and compositions of Hsp70 protein do not share a special technical feature". As amended by this amendment, the instant claims lack a special technical feature as they are not novel over the art as evidenced by the art rejections below. Accordingly the elections of species requirement is maintained.

5. Claim 37 is objected to because of the following informalities: the claim recites "an isolated" twice. Appropriate correction is required.

6. The rejection of claims 31-43, 45-48, 50-56, and 58-60 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained for the following reasons of record. Claims 31, 42, 50 and 55 recite "derivatives" of Hsp70 or the fragment of Hsp70 from amino acid 384-641, or amino acid sequences having 70% homology to the aforesaid fragment. The specification neither defines or provides examples of a "derivative", therefore, the metes and bounds of the claims with respect to the constitution of a derivative cannot be ascertained.

Applicant argues that derivative is defined on page 3, three lines up from the bottom to page 4, line 4. this has been considered but not found persuasive. The cited text states that the term derivative comprises both derivatives of the Hsp70 protein as well as derivatives of the C-terminal fragment as far as the derivatives exhibit the functions of the invention. Preferably, such derivatives exhibit the same three dimensional structures as Hsp70 or its C-terminal fragment and can be produced by peptidomimetics. It is noted that the characteristics of having the same three dimensional structure as Hsp70 are not a limiting definition of the term derivative, but preferred embodiment. The metes and bounds of the structural attributes which can be construed as a derivative of Hsp70 are not defined by the specification.

7. The rejection of claims 30-42, 45-48, 50-56 and 58-60 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained for reasons of record. of section (B) of the previous Office action.

With regard to section (A) of the rejection, applicant has canceled claims 44 and 57, but persists in arguing that the specification supports this feature of administration referring to page

9, lines 1-2 wherein it is stated that "the corresponding period before the administration of the hsp70 should be at least 3-24 hours". this has been considered, but not found persuasive. The claims which were rejected for new matter were drawn to the method of claim 42 or the method of claim 55 wherein the administration is carried out for at least 3 hours. The length of the administration has no nexus with the period before the administration, as cited by the text. Cancellation of claims 44 and 57 has rendered the rejection moot.

(B)As drawn to derivatives of the amino residues 284-641 of SEQ ID NO:1, proteins having 70% homology to amino acids 384-641 of SEQ ID NO:1, and derivatives thereof.

Claims 31-42, 44-48 and 50-60 are drawn to a genus of proteins comprising derivatives of proteins having the amino acid sequence from residues 384-681 of SEQ ID NO:1 and proteins having at least 70% homology to amino acid residues 384-641 of SEQ ID NO:1 and derivatives thereof, as well as method claims dependent upon these products. The specification sets forth Hsp70 as SEQ ID NO:1, and teaches that residues 384-641 of SEQ ID NO:1 are responsible for the activation of NK cells into cytotoxic cells. The specification teaches that the Hsp70 protein is a heat shock protein which is differentially expressed on many types of cancerous cells. The specification contemplates methods of activating NK cells by means of proteins having at least 70% homology to amino acid residues 384-681 of SEQ ID NO:1. The specification also contemplates "derivatives" of Hsp70 or the fragment of Hsp70 from amino acid 384-641, or amino acid sequences having 70% homology to the aforesaid fragment. The specification states on page that the term "derivative" encompasses both derivatives of the Hsp70 protein as well as derivatives of the C-terminal fragment as far as the derivatives exhibit the function of the invention. However, the specific limitation with regard to said function is missing from the claims, and further, the specification provides no teachings regarding the structural attributes of what constitutes a "derivative" of the claimed proteins which would serve to discriminate between members of the claimed genus and species which were not part of the claimed genus. The genus is therefore highly variant encompassing widely ranging structural deviations from Hsp70 and the amino acid sequence comprising residues 284-681 of SEQ ID NO:1, wherein said deviations could include fusions with any other amino acid sequence, alterations of the protein backbone, coupling with any known chemical which reacts with amino acid sequences, proteolytic fragments of the amino acid sequence comprising residues 284-641 of SEQ ID NO:1,

enzymatic modification of said amino acid sequence, and amino acid substitutions, deletions and additions to residues 281-641 of SEQ ID NO:1. The disclosure of SEQ ID NO:1 is inadequate written description for this multitude of species encompassed by the claims..

The specification states on page 4, that amino acid sequence identity to the Hsp70 protein means that at least 70% of the amino acids are identical when the two amino acid are aligned, wherein one of the aligned sequences is the C-terminus of Hsp70. The specification also states that the invention encompasses sequences which have 70% identical amino acids, but differ by gaps when aligned with the Hsp70 sequence, and that said gaps can occur in the homologous molecule or in the reference molecule. Thus, the specification teaches that 70% homologous sequences encompasses amino acid sequences which have substitutions, deletions and additions of amino acids from amino acid residues 384-681 of SEQ ID NO:1. No further description of any variant protein structure is made by the specification and no embodiment limiting the number of amino acid substitutions, deletions or additions is present in the specification or claims. Thus the scope of the genus includes numerous structural variants and the genus is highly variant because s significant number of structural differences between genus members is permitted. Neither the specification or claims indicate distinguishing structural and functional characteristics shared by members of the genus that could serve to distinguish proteins in the genus from other proteins not in the genus.

The general knowledge and skill in the art do not supplement the omitted description of derivatives and proteins comprising variants of residues 384-681 of SEQ ID NO:1, and derivatives thereof, because specific, not general, guidance is what is needed. Since the disclosure fails to identify the structural and functional attributes of the genuses, and because the genuses are highly variant, SEQ ID NO:1 alone is insufficient to describe the claimed genus. Furthermore, one of skill in the art would conclude that the specification also failed to describe a number of species representative of the "derivative" genus and the "70% homologous" genus. Thus, applicant was not in possession of the either the claimed "derivative" or "homolog" genuses.

With regard to section (B) of the rejection, applicant argues that it is unclear whether the issue relates to written description or enablement. Applicant construes that because the rejection was based on the multitude of species allegedly encompassed by the claims that the rejection

was for scope of enablement. this was considered but not found persuasive. The rejection is clearly set forth under written description "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention" No issues regarding unreliability of the art, lack of working examples, or undue experimentation commensurate with a scope rejection were set forth. It is noted that applicant did not present any argument regarding support for the variant genuses on which the method claims and the composition claim are based. Applicant has amended claim 31 to state functional limitations of the isolated proteins, fragment, polypeptide and derivates, however, because the genus comprising "derivatives" is without a structural limitation, the genus remains highly variant, tolerating members which have numerous structural alterations in relation to Hsp70. Thus, the disclosure of Hsp70 does not adequately describe the genus. Further, claims 42 and 50 have not been amended

8. The rejection of claims 50-53 , 55, 56 and 58-60 under 35 U.S.C. 102(b) as being anticipated by Srivastava (WO 97/10001) is maintained for reasons of record..

Claim 50 is drawn in part to a pharmaceutical composition comprising the Hsp70 protein or a pharmaceutical composition comprising the amino acids of 384-681 of SEQ ID NO:1, and a pharmaceutically acceptable carrier, excipient or diluent. Claim 51 embodies the composition of claim 50, wherein said protein or fragment is present at a concentration of about 10 micrograms/ml to 1000 micrograms per ml. Claim 52 embodies the composition of claim 50 wherein said protein or fragment is of human origin. Claim 53 specifically embodies the composition of claim 50, wherein said protein or fragment is recombinant.

Claim 55 is drawn to a method of in vivo activation of the immune system in a patient in need thereof comprising administering to said patient a pharmaceutically effective amount of an Hsp70 protein or a C-terminal fragment of Hsp70 comprising amino acid residues 284-681 of SEQ ID NO:1. Claim 56 embodies the method of claim 55 wherein said patient is suffering from cancer. Claim 58 embodies the method of claim 56, wherein said administration further

comprises addition of a cytokine, claim 59 specifies that the cytokine in an interleukin. Claims 60 embodies the interleukins of Il-2, Il-12 and Il-15.

Srivastava discloses a method for eliciting an immune response in an individual in whom the treatment if cancer is desired by administering a composition comprising a heat shock protein, wherein the heat shock protein is human Hsp70 (page 14, line 33 to page 15, line 2 and lines 29-31, page 43, line 15 to page 44, line 12). Srivastava discloses that said method further comprises the administration of biological response modifiers such as interferons alpha and gamma, interleukins 2, 4, and 6, tumor necrosis factor or other cytokine growth factors in combination with the heat shock protein (page 12, lines 18-22). Srivastava does not specifically state that Hsp70 activates NK cells, however the administration of Hsp70 to a mammal in an amount sufficient to elicit an immune response for the treatment of cancer would inherently activate NK cells in said individual.

Srivastava discloses pharmaceutical compositions comprising Hsp70 in physiologically acceptable solvents for the administration to mammals (page 38, lines 32-35 and page 39, line 30 to page 42, line 15). Srivastava further discloses a composition comprising five to ten micrograms of the Hsp70 protein in 100 microliter, which is the same as 50 micrograms/ml to 100 micrograms/ml and thus falls within the claimed range of 10 micrograms/ml to 1000 micrograms/ml (page 36, lines 25-32). Srivastava does not disclose the recombinant Hsp70 protein, however, the Hsp70 protein isolated by Srivastava would have the same inherent properties as the recombinant protein.

Applicant argues that the disclosure of Srivastava is different from the instant invention as Srivastava administers the Hsp70 protein in a complex with an antigen, and that the result was that immunity was not induced to antigenically distinct cells. It is noted that on page 18, Srivastava states that the composition "stimulates that immunocompetence of the host individual and elicits specific immunity against preneoplastic or neoplastic cells". However, the elicitation of specific immunity against "antigenically distinct cells" is not a limitation of the claims. Further, amendment of the claims to recite "isolated" Hsp70 protein does not render this rejection moot as Srivastava isolated Hsp70 peptide complexes from cells. The specification does not provide a definition of isolated which would exclude the isolation of Hsp70 as a complex.

9. The rejection of claims 50-56 and 58-60 under 35 U.S.C. 102(e) as being anticipated by Multhoff et al (U.S. 6,261,839) is maintained for reasons of record.. Claim 54 is drawn to a pharmaceutical composition comprising NK cells activated by the method of claim 31. Multhoff et al disclose the method of ex vivo activation comprising contacting fractionated NK cells obtained from peripheral blood with target cells selected from the group consisting of leukemic cells, metastasized solid tumor cells and metastasized lymphoma cells (claims 1-18), wherein said target cells are induced to over express the Hsp70 protein. Multhoff et al disclose that enhanced activation of Hsp70 specific NK cells can be achieved by addition of interleukin-2 in a low dose (column 7, lines 65-67). Multhoff et al also disclose a method of treating a subject having cancer comprising administering the NK cells activated by incubation with the target cells expressing the Hsp70 protein (claims 19 and 20). Multhoff et al doses not disclose the ex vivo activation of NK cell by contacting with isolated Hsp70, however, it appears that the composition of NK cells activated by the method of Multhoff et al would be the same as the pharmaceutical composition of cells activated by the method of claim 31, thus fulfilling the specific embodiments of claim 54.

Applicant argue that the '839 patent does not anticipate the instant claims as the patent teaches the treatment of NK cells with heat and then with a lysophosphingolipid or edelfosine which differs from the instant invention which exposes NK cells to isolated Hsp70. This has been considered but not found persuasive. Multhoff et al)'839) disclose that expression of Hsp70 in target cells is induced by heat treatment followed by the addition of a compound which further increases membrane bound Hsp70 in target cells. It is noted that the patent teaches that the Hsp70 protein is being induced on the target cells and not on the NK cells (column 2, lines 47-53). Thus, Multhoff et al disclose NK cells activated by Hsp70 expression in target cells which is not excluded by claims 50-56 and 58-60 which have not been amended to recite "an isolated " Hsp70 protein.

10. Claims 31-37, 39-43, 45-48 , 54-56 and 58-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Multhoff et al (Blood, 1995, Vol. 86, pp. 1374-1382, cited in the previous Office action) in view of Srivastava (WO 97/10001) and Multhoff et al (Journal of

Immunology, 1997, Vol. 158, pp. 4341-4350, cited in the previous Office action) and the abstract of Boltzer et al (Cell Stress and Chaperones, 1998, Vol. 3, pp. 6-11, cited in the previous Office action)..

Claim 31 is drawn in part to a method for the ex vivo activation of NK cells comprising contacting NK cells in a physiological suspension with an isolated protein comprising a derivative of the fragment consisting of amino acid residues 284 to 361 of SEQ ID NO:1. Claim 32 embodies the method of claim 31 wherein said activation comprises an increase in cytotoxicity. Claim 33 embodies the method of claim 33 wherein said physiological suspension containing NK cells comprises a peripheral mononuclear blood cell fraction. Claim 34 comprises the method of claim 31 wherein said suspension further comprises cells expressing cell-surface Hsp70. Claim 35 embodies the method of claim 34 wherein said expressing cells comprise diseased cells from a patient. Claim 36 specifies that the diseased cells are selected from tumor cells. Claim 37 is drawn to the method of any one of claims 31-36 wherein said contacting is carried out for at least 3 hours. Claim 37 embodies the method of claim 36, wherein the contacting is carried out for at least 3 hours. Claim 39 is drawn to the method of claim 37, wherein the conditions further comprise addition of a cytokine. Claim 40 specifies that the cytokine is an interleukin. Claim 41 specifically embodies the interleukins of Il-2, Il-12 and Il-15. Claim 42 is drawn to a method for the in vivo activation of the immune system of a patient in need comprising administering to said patient a pharmaceutically effective amount of NK cells obtained by the method of claim 37 and optionally administering to said patient a pharmaceutically effective mount of Hsp70 protein. Claim 43 embodies the method of claim 42 wherein said patient is suffering from a cancerous disease. Claim 45 embodies the method of claim 42 wherein said administration further comprises the addition of a cytokine. Claim 46 specifies the cytokine as an interleukin. Claim 47 specifies that the interleukin is selected from the group consisting of Il-2, Il-12, and Il-15. Claim 48 embodies the method of claim 43 wherein said cancerous disease is tumors, solid tumors, metastatic tumors, leukemias and lymphomas.

Multhoff et al (1995) teach a method for the ex vivo activation of NK cells comprising contacting an Il-2 stimulated NK cells obtained from fractionation of peripheral blood (page 1375, second column, under the heading "Separation of effector cell populations") with human sarcoma cells (page 1375, first column, under the heading "Cell culture of normal and malignant

cells"). The sarcoma cell line used by Multhoff are derived from derived from patients suffering from cancer and thus satisfy the specific embodiment of claims 35 and 36. Multhoff et al disclose that the sarcoma cells express Hsp72, which is a heat-inducible form of Hsp70 and that the Hsp72 is a cell surface determinant for NK cells (page 1380, first column, line 20 to second column, line 4). Thus the specific embodiment of claim 34 is fulfilled. Multhoff et la teach that Hsp72 cell surface expression on the sarcoma cells correlates with lysis by NK cells (figures 1 and 2). The specific lysis indicated in figures 1 and 2 is indicative of an increase in cytotoxicity, thus fulfilling the specific embodiment of claim 32. Multhoff et al teach the incubation of Il-2 activated NK cells with target cells , wherein the contacting is carried out for 4 hours, fulfilling the specific embodiment of claims 37 and 40-41 (page 1376, first column, under the heading "Cytotoxicity assay"). Multhoff et al suggest that the heat inducible Hsp72 epitope is a positive recognition structure for NK cells (page 1380, first column, lines 20-23). It is noted that the metes and bounds of Hsp70 cannot be determined for the reasons set forth in the rejection under 112, second paragraph, and thus, Hsp72 can be construed as a C-terminal fragment of Hsp70 as it embodies a derivative. Multhoff et al do not teach the concurrent or subsequent administration of a Hsp70 protein in addition to the activated NK cells of claim 37. Multhoff et al (1995) do not teach the ex vivo activation of NK cells comprising the administration of an isolated C-terminal fragment of Hsp70, a method for the in vivo activation of the immune system in a patient comprising the administration of said activated NK cells, , or an amount of the C-terminal fragment of Hsp70, or a pharmaceutical composition comprising the C-terminal fragment of Hsp70 and a pharmaceutically acceptable carrier.

Multhoff et al (1997)disclose a method for the ex vivo activation of NK cells comprising contacting an Il-2 stimulated NK cells obtained from fractionation of peripheral blood with colon carcinoma cells. The colon carcinoma cells are a cell line named CX derived from a patient and thus satisfy the specific embodiments of claims 35 and 36. Multhoff et la disclose that Hsp72 cell surface expression of the CX2 and CX+ colon carcinoma cells strictly correlates with lysis by NK cells (page 4344, under the heading "Cytotoxicity assay", figure 7, page 4349, first full paragraph, and third full paragraph, "on NK cells, one must consider HSP72 expression as an additional possible structure that determines the susceptibility of tumor target cells to lysis is mediated by an NK population"), thus the specific embodiment of claim 34 is fulfilled. Multhoff

et al identify Hsp72 cell surface expression as an immunogenic determinant for NK mediated lysis of autologous tumor cells (page 4341, second column, last sentence). Multhoff et al teach that no additional heat-inducible factor is necessary for the recognition mechanism mediated by Hsp72-specfic NK cell population (page 4349, first column, lines 18-22). Muthjoff et al teach that Ab binding to MHC class I had no inhibitory effect on the lysis of tumor cells, thus suggesting that recognition of MHC class I was not part of the NK-induced cytotoxicity (page 4349, lines 24-35). The specific lysis indicated in figure 2 is indicative of an increase in cytotoxicity, thus fulfilling the specific embodiment of claim 32.

Botzler et al teach that the CX cell line expresses the Hsp70 antigens and that the C-terminus of Hsp70 is localized extracellularly. Boltzer et al teach that the C-terminal region of Hsp70 contains at least one alpha helix which is located extracellularly and might be of importance for an NK-mediated anti-tumor response.

Srivastava (WO 97/10001) teaches the specific embodiments of claims 50-53 and 55, 56 and 58-60 for the reasons set forth in section 10 above. Srivastava teach the in vivo activation of the immune system in a patient in need of comprising administration of the Hsp70 protein useful for the treatment of leukemia, lymphoma, solid tumors and metastatic tumors (page 43, line 16 to page 44, line 5 and lines 16 to page 46, line 7).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to activate NK cells ex vivo comprising the administration of Hsp72 complexed with tumor antigen or the C-terminus of Hsp72 complexed with a tumor antigen and administer said NK cells as a pharmaceutical composition to a patient having a tumor which expresses Hsp72, or administer the isolated Hsp72 protein complexed with tumor antigen to or a fragment comprising the C-terminus of Hsp72 complexed with an antigen to a patient having a tumor which expresses Hsp72. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Multhoff et al (1995) on the cell surface Hsp72 epitope as a positive recognition structure for NK cells, the teachings of Multhoff et al (1997) that no other heat inducible factor was necessary for the recognition mechanism mediated by the NK cells activated by tumor Hsp72, and the teachings of Boltzer et al on the extracellular location of the C-terminus of the Hsp70 protein and the suggestion by Boltzer et al that said extracellular C-terminus is important in NF cell recognition.

Further It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the administration of a pharmaceutical composition comprising said ex vivo activated NK cells with the method of inducing an immune response comprising the administration of the Hsp72 protein. The instant situation is amenable to the type of analysis set forth in *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to produce a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been taught individually in the prior art. Applying the same logic to the instant process claims, it would be obvious to one of skill in the art to combine two methods to induce an immune response in order to treat an individual with cancer. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Srivastava on the therapeutic efficacy of treating cancer by the administration of the isolated Hsp70 protein complex.

Applicant argues that none of the prior art references teach the specific embodiment of using a isolated Hsp70, but instead teach complexes and membrane bound constituents, and the exchange of Hsp72 for Hsp70 does not achieve the invention as claimed. Applicant argues that there is no reasonable expectation that exchange of Hsp72 for Hsp70 would lead to the tangible results as claimed. This has been considered but not found persuasive. It is noted that claims 50-53 and 55, 56 and 58-60 do not specify that the Hsp70 protein be an isolated protein. Further, when given the broadest reasonable interpretation, Hsp72 reads on a C-terminal fragment of Hsp70, wherein said fragment is a derivative of amino acids 384-641 or a derivative of an isolated polypeptide having 70% homology to amino acids 384-641. The specification states that the derivatives of Hsp comprise derivatives which "exhibit the functions of the invention" (page 3, lines 32-33). It appears that Hsp72 exhibits the functions of the invention as it activates NK cells. Further, Multhoff et al (1997) teaches that Hsp72 is a member of the Hsp70 protein family (abstract) , thus it would be expected that Hsp70 and Hsp72 would have similar properties and functions. Applicant argues that the use of membrane bound Hsp72 would appear to "teach away" from the instant invention and that an artisan would expect complex or auxiliary molecules would be required for the NK cell activation. This has been considered but not found

persuasive. It is taught by Multhoff et al (1997) that no additional heat-inducible factor is necessary for the recognition mechanism mediated by Hsp72-specfic NK cells and that Ab binding to MHC class I had no inhibitory effect on the lysis of tumor cells, thus suggesting that recognition of MHC class I was not part of the NK-induced cytotoxicity. Further Boltzer et al teaches that the C-terminus of Hsp70 is presented on the cell surface as a single alpha helix. thus, both references do not provide any teachings to indicate that Hsp72 would require cell membrane components to activate NK cells.

Applicant argues that *In re Kerkhoven* does not apply to the instant case because in the cited case there was no differnce between the components described in the art and the components recited in the claims. This has been considered but not found persuasive. The combination of the prior art references renders obvious the administration of the isolated Hsp70 protein as part of a complex. The claims do not contain a limitation which would exclude the adminstration of the isolated Hsp70 protein in a complex. Therefore, it is concluded that the prior art components are within the scope of the components of the claim and the objection to the application of *In re Kerkhoven* is rendered moot.

11. The rejection of claims 55 and 56 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19 and 20 of U.S. Patent No. 6,261,839 is maintained for reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 19 and 20 of the '839 patent anticipate claims 55 and 56 as the method of administering NK cells of the patent, would inherently comprise a pharmaceutically effective amount of a Hsp70 protein and claim 55 has not been amended to recite "isolated" Hsp70 protein..

Applicant argues that the rejection is defective because there are no reasons why a person of ordinary skill in the art would conclude that the invention in the claim at issue is an obvious variation of the claim in the patent, and because the examiner noted that the claims of the patent anticipate the instant claims, the rejection is therefore defective. This has been considered but not found persuasive. As stated in the prior Office action an obviousness-type

double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentable distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g. *In re Berg*, 140 F. 3d 1428, 46 USPQ2d 1226 (Fed Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Thus the rejection of a claim under obviousness-type double patenting because it is anticipated by a prior patented claim constitutes a proper rejection.

12. All other rejections and objections as set forth in Paper No. 16 are withdrawn.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703)

308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
9/24/03

Karen A. Canella